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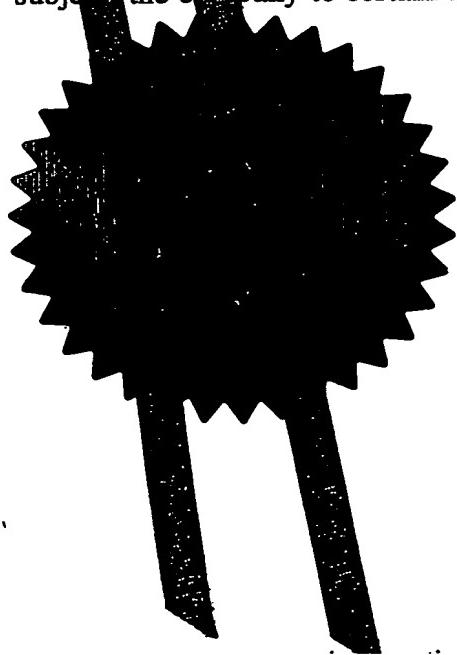
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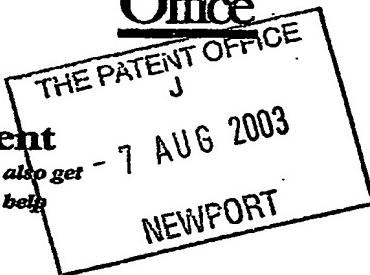
R. Mahoney
16 January 2004

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PAUL 3 E828070-1 DD2944
P007700 0 00 03/08/07**Request for grant of a patent**

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1. Your reference

SMC 60614/GB/P1

2. Patent application number

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- 7 AUG 2003

0318515.4

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)

Avecia Limited
Hexagon House
Blackley
Manchester, M9 8ZS

Patents ADP number (*if you know it*)

07764137001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

Compounds and Process

5. Name of your agent (*if you have one*)

REVELL, Christopher

"Address for service" in the United Kingdom to which all correspondence should be sent (*including the postcode*)

Avecia Limited
Hexagon House
PO Box 42
Blackley
Manchester M9 8ZS

Patents ADP number (*if you know it*)

6969885001

7764137001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (*if you know it*) the or each application number

Country	Priority application number (<i>if you know it</i>)	Date of filing (day / month / year)
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer 'Yes' if:*

- a) *any applicant named in part 3 is not an inventor, or*
 - b) *there is an inventor who is not named as an applicant, or*
 - c) *any named applicant is a corporate body.*
- See note (d))*

Patents Form 1/77

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Description	6
Claim(s)	4
Abstract	1

Drawing(s)

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Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents
(please specify)

I/We request the grant of a patent on the basis of this application.

Signature

Avecia Limited Authorised Signatory

Date 6th AUGUST, 2003

11. 12. Name and daytime telephone number of person to contact in the United Kingdom

K.M.Pinder/G.Terry 0161 721 1361/2

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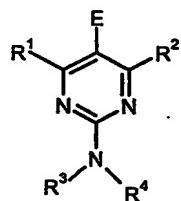
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COMPOUNDS AND PROCESS

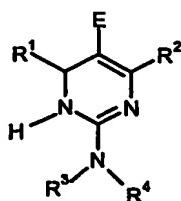
The present invention concerns a process for the preparation of pyrimidines and intermediate compounds useful in the preparation thereof.

According to a first aspect of the present invention, there is provided a process for
5 the preparation of a compound of Formula (1):



Formula (1)

- 10 which comprises
- a) reacting a compound of formula $R^1\text{-CO-CH}_2\text{-E}$ with a compound of formula $R^2\text{-CHX}^1\text{X}^2$ in the presence of a compound of formula $R^3R^4\text{N-C(=NH)NH}_2$ and a catalyst, thereby to form a dihydropyrimidine; and
 - 15 b) oxidising the dihydropyrimidine produced in step a) to form the compound of Formula (1)
- wherein
- R^1 is H or an alkyl group;
 - R^2 is H or an alkyl or aryl group;
 - 20 R^3 and R^4 are each independently H, alkyl, aryl, a group of formula $R^5\text{SO}_2^-$, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring;
 - E is an electron withdrawing group; and
 - X¹ and X² are each independently leaving groups, or X¹ and X² together represent =O.
- 25 Dihydropyrimidines formed in step a) can be represented by the Formula (2):



Formula (2)

It will be recognised that the compounds of Formula (2) can exist in a number of tautomeric forms in which the double bonds are delocalised into other positions in the molecule, notably into different positions around the pyrimidine ring.

5 Alkyl groups which may be represented by R¹ include linear, branched and cyclic alkyl groups commonly comprising from 1 to 8 carbon atoms. Preferred cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Preferred linear and branched alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl and tert-butyl groups. Most preferably, R¹ represents isopropyl.

10 Alkyl groups which may be represented by R² are as described above for R¹.

15 Aryl groups which may be represented by R² include both homoaryl and heteroaryl groups, and commonly comprise at least one 5 to 7 membered aromatic ring. Examples of aryl groups include phenyl, naphthyl and pyridyl groups. Most preferably, R² represents a phenyl group.

20 Alkyl and aryl groups which may be represented by R³, R⁴ and R⁵ are as described above for R¹ and R². When one of R³ or R⁴ represents a group of formula R⁵SO₂⁻, it is preferably a mesyl or tosyl group. In certain preferred embodiments, R³ represents methyl and R⁴ represents mesyl. In other preferred embodiments, either or both of R³ and R⁴ are H.

25 Alkyl and aryl groups which may be represented by R¹, R², R³, R⁴ and R⁵ may be unsubstituted or substituted by one or more substituents. Examples of substituents include optionally substituted alkoxy (preferably C₁₋₄-alkoxy), optionally substituted alkyl (preferably C₁₋₄-alkyl), optionally substituted aryl (preferably phenyl), optionally substituted aryloxy (preferably phenoxy), optionally substituted heterocycl, polyalkylene oxide (preferably polyethylene oxide or polypropylene oxide), carboxy, phosphato, sulpho, nitro, cyano, halo, especially chloro and fluoro, ureido, -SO₂F, hydroxy, ester, -NR^aR^b, -COR^a, -CONR^aR^b, -NHCOR^a, carboxyester, sulphone, and -SO₂NR^aR^b wherein R^a and R^b are each independently H, optionally substituted alkyl (especially C₁₋₄-alkyl) or optionally substituted aryl (preferably phenyl), or, in the case of -NR^aR^b, -CONR^aR^b and -SO₂NR^aR^b, R^a and R^b together with the nitrogen atom to which they are attached may represent an aliphatic or aromatic ring system. Optional substituents for any of the substituents described may be selected from the same list of substituents.

30 Electron withdrawing groups which may be represented by E include nitro groups; nitrile groups; perhaloalkyl groups, such as trifluoromethyl and pentafluoroethyl; ester groups, especially alkyl carboxylate groups; sulphonamide groups; keto groups; amide groups; and aldehyde groups.

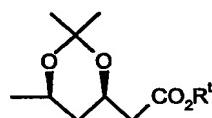
35 E may also represent a group of formula -CHX^aX^b, wherein X^a and X^b each independently represents a halo, especially a chloro or bromo group, an alkoxy group, especially a C₁₋₄alkoxy, such as a methoxy or ethoxy group, an alkylthio group, especially a C₁₋₄alkylthio group, or X^a and X^b are linked to form a cyclic acetal or thioacetal

commonly comprising, with the carbon to which X^a and X^b are bonded, from 5 to 7 atoms in the ring. When E represents a group of formula $-CHX^aX^b$, it is preferred that X^a is the same as X^b .

Further groups which may be represented by E are groups of formula $-CH_2E^2$,
 5 wherein E^2 represents halo, especially bromo or chloro, or a phosphorus-containing moiety, such as a phosphate ester, for example of formula $-OP(=O)(OR^c)_2$, a phosphonate ester, for example of formula $-P(=O)(OR^c)_2$, a phosphite ester, for example of formula $-P(OR^c)_2$, a phosphine, for example of formula $-P(R^c)_2$, or a phosphine oxide, for example of formula $-P(=O)(R^c)_2$ in each of which R^c represents an alkyl, such as a C₁₋₄
 10 alkyl, or an aryl, such as a phenyl, group. When E^2 represents a phosphorus-containing moiety, it is preferably a phosphonate ester of formula $-P(=O)(OR^d)_2$ wherein R^d represents methyl, ethyl or phenyl.

E may also represent a group of formula $-CR^x=CR^yR^z$, wherein R^x , R^y and R^z each independently represent H, alkyl or aryl. Preferably, R^x and R^y represent H, and R^z represents an optionally substituted C₁₋₅ alkyl chain. R^z is preferably substituted by two hydroxy groups, commonly present as a protected 1,3-dihydroxy moiety. R^z preferably comprises a terminal carboxyl group, especially a carboxy ester group. R^z is most preferably a group of formula:

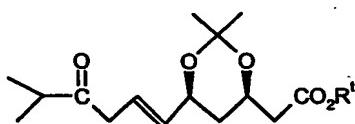
20



wherein R^t is an alkyl group, preferably a tert-butyl group.

25

A particular compound of formula R¹-CO-CH₂-E is of formula:



wherein R^t is an alkyl group, preferably a tert-butyl group.

30

Preferably, E represents a group of formula $-CO_2(C_{1-4}\text{alkyl})$, and especially $-CO_2\text{Me}$.

Leaving groups which can be represented by X¹ and X² include chloro, bromo and iodo, especially chloro, groups, and alkoxy groups, especially C₁₋₄alkoxy, such as methoxy, groups. Commonly when X¹ and X² are leaving groups, either both are selected

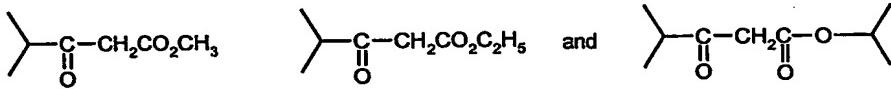
from chloro, bromo or iodo, or both are alkoxy. It is most preferred that X¹ and X² together represent =O.

In certain aspects of the present invention, in place of the compound of formula R¹-CO-CH₂-E, a compound of formula R¹-CO-CH=CH-N(R^q)₂ is employed, wherein R¹ is as previously defined, and each R^q independently is an alkyl, preferably a C₁₋₄ alkyl, group, an aryl group, preferably a phenyl group, or the moiety N(R^q)₂ represents a 5 to 7 membered heterocyclic group, such as a pyrrolidine, piperidine or morpholine group.

Oxidising agents which may be employed in the process according to the present invention include those oxidising agents known in the art to oxidise dihydropyrimidines to pyrimidines. Examples of suitable oxidising agents include quinones, particularly substituted benzoquinones such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; transition metal oxidants such as ceric ammonium nitrate or sulfate, barium manganate, cadmium chloride and manganese dioxide; metallic oxidants, such as palladium on charcoal or other suitable platinum group metals; elemental sulfur; oxygen, especially atmospheric oxygen; and nitrosylsulfuric acid.

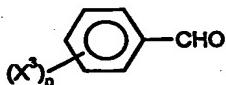
Preferred compounds of formula R¹-CO-CH₂-E are compounds of formula (C₁₋₄alkyl)-CO-CH₂CO₂R⁶, wherein R⁶ represents a C₁₋₄ alkyl group, especially a methyl, ethyl or isopropyl group. Most preferred compounds of formula R¹-CO-CH₂-E are compounds of formulae:

20



Compounds of formula (CH₃)₂CH-CO-CH₂-CO₂-C₃H₇, preferably (CH₃)₂CH-CO-CH₂-CO₂-CH(CH₃)₂, form another aspect of the present invention. Such compounds may be prepared by methods analogous to those known in the art for the preparation of similar compounds, such as methyl isobutyrylacetate and ethyl isobutyrylacetate.

Preferred compounds of formula R²-CHX¹X² are compounds of formula:



30 wherein X³ represents halo, and n is 0 or 1-5. Preferably X³ is chloro or fluoro, alkyl, preferably methyl, or alkoxy, preferably methoxy. Most preferably n is 1, and X³ is present at the 4-position. Especially preferred is 4-fluorobenzaldehyde.

Preferred compounds of formula R³R⁴N-C(=NH)NH₂ are guanidine, methylguanidine and N-methyl-N-mesylguanidine. The compounds of formula R³R⁴N-C(=NH)NH₂ can be employed as the free base, but in many embodiments are advantageously employed as a salt, especially a hydrochloride salt.

Catalysts which can be employed in the present invention include bases and acids.

Bases which can be employed in the process of the present invention are preferably inorganic bases. Examples of inorganic base include alkali and alkaline earth metal carbonates and hydrogencarbonates, particularly sodium or potassium carbonate and most preferably sodium or potassium hydrogencarbonate.

Acids which can be employed in the process of the present invention include both protic and Lewis acids. Examples of protic acids include mineral acids, such as hydrochloric, nitric and sulphuric acids and polyphosphate ester, or organic acids such as p-toluenesulfonic acid. Examples of suitable Lewis acids include FeCl_3 , NiCl_2 , boron trifluoride etherate and InCl_3 . When a Lewis acid is employed, a protic acid such as HCl, may also advantageously be present.

Step a) of the process according to the present invention preferably employs a solvent which is inert under the reaction conditions employed. In may embodiments, a polar solvent is employed, preferably a polar aprotic solvent, for example including dichloromethane, dimethylsulphoxide and tetrahydrofuran. Preferred solvents are amides, such as N-methylpyrrolidinone and especially dimethylformamide.

Step b) of the process preferably employs a solvent which is inert under the reaction conditions employed. The solvent is selected according to the nature of the oxidising agent employed, and may include the solvents described above for step a). Further solvents which may be employed in step b) include non-polar solvents, for example hydrocarbons, such as toluene.

Compounds of Formula (2) and tautomers thereof are novel, and accordingly form a second aspect of the present invention.

Step a) of the process according to the first aspect of present invention forms a third aspect of the present invention.

Step b) of the process according to the first aspect of present invention forms a fourth aspect of the present invention.

When it is desired to produce a compound of formula (1) wherein one or both of R^3 and R^4 is not H, it will be recognised that the alkyl, aryl or SO_2R^5 moieties, particularly methyl and mesyl moieties, may be present in the compound of formula $\text{R}^3\text{R}^4\text{N}-\text{C}(=\text{NH})\text{NH}_2$, may be introduced into a compound of formula (2) prepared where R^3 and R^4 are both H, prior to the oxidation in step b), or may be introduced into a compound of formula (2) prepared where R^3 and R^4 are both H.

The present invention is illustrated further, without limitation, by the following example.

Example

- a) A 100 ml two neck round bottom flask equipped with a condenser and connected to a nitrogen line was charged with p-fluorobenzaldehyde (0.57ml, 5mmol), MIBA (0.79g, 5.5mmol), guanidine hydrochloride (1.19g, 12.5mmol), potassium carbonate (2.76g, 40mmol) and 10 ml of anhydrous dimethylformamide. This mixture was stirred and
5 heated at 70°C for 20h. The reaction mixture changed from colourless to yellow during this time. After cooling, dimethylformamide was removed under vacuum and the residue partitioned between brine (50ml) and ethyl acetate (200ml). The aqueous phase was washed with ethyl acetate (200ml) and the combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed under vacuum to obtain 1g of
10 yellow solid. ^1H NMR and LC showed methyl 2-amino-6-(4-fluorophenyl)-4-isopropyl-3,4-dihydropyrimidine-5-carboxylate as the major component (82%). This sample was characterised by comparison with a previously prepared standard.
- b) A 25 ml three neck round bottom flask evacuated and back-filled with nitrogen was
15 charged with methyl 2-amino-6-(4-fluorophenyl)-4-isopropyl-1,4-dihydropyrimidine-5-carboxylate (100 mg) and 15 ml of anhydrous THF. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (135 mg, 0.45 mmol) was added under nitrogen. The red solution was stirred at room temperature. After 40 min, methyl 2-amino-6-(4-fluorophenyl)-4-isopropylpyrimidine-5-carboxylate was observed by HPLC and LC-MS. The product was
20 identified by comparison with a standard of high purity prepared by a different chemical route. Both samples co-eluted by HPLC and showed the same ions by positive and negative electrospray mass spectrometry.

CLAIMS

1. A process for the preparation of a compound of Formula (1):



5

Formula (1)

which comprises

- 10 a) reacting a compound of formula $R^1\text{-CO-CH}_2\text{-E}$ with a compound of formula $R^2\text{-CHX}^1\text{X}^2$ in the presence of a compound of formula $R^3R^4\text{N-C(=NH)NH}_2$ and a catalyst, thereby to form a dihydropyrimidine; and

- b) oxidising the dihydropyrimidine produced in step a) to form the compound of Formula (1).

15 wherein

R^1 is H or an alkyl group;

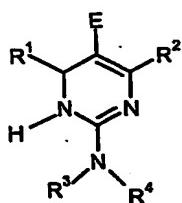
R^2 is H or an alkyl or aryl group;

R^3 and R^4 are each independently H, alkyl, aryl, a group of formula $R^5\text{SO}_2^-$, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring;

20 E is an electron withdrawing group; and

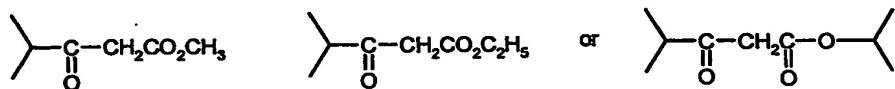
X^1 and X^2 are each independently leaving groups, or X^1 and X^2 together represent =O.

- 25 2. A process according to claim 1, wherein the dihydropyrimidine is represented by the Formula (2), and tautomers thereof:

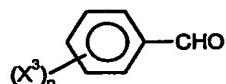


Formula (2)

3. A process according to claim 1 or claim 2, wherein the compound of formula $R^1-CO-CH_2-E$ is a compound of formulae:



- 5 4. A process according to any preceding claim, wherein the compound of formula $R^2-CHX^1X^2$ is a compound of formula:



wherein X^3 represents halo, and n is 0 or 1-5, and preferably 4-fluorobenzaldehyde.

- 10 5. A process according to any preceding claim, wherein the compound of formula $R^3R^4N-C(=NH)NH_2$ is guanidine, methylguanidine or N-methyl-N-mesylguanidine.

- 15 6. A process according to claim 5, wherein the compound of formula $R^3R^4N-C(=NH)NH_2$ is employed as a hydrochloride salt.

7. A process according to any preceding claim, wherein the catalyst is a base, preferably an alkali or alkaline earth metal carbonate and hydrogencarbonate.

- 20 8. A process according to any preceding claim, wherein the oxidising agent is a quinone.

9. A compound of Formula (2), and tautomers thereof:



Formula (2)

wherein

R^1 is H or an alkyl group;

30 R^2 is an H or an alkyl or aryl group;

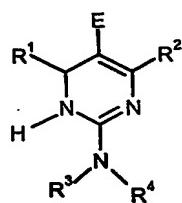
R^3 and R^4 are each independently H, alkyl, aryl, a group of formula $R^5SO_2^-$, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring; and

E is an electron withdrawing group.

5 10. A compound according to claim 9, wherein R^1 represents isopropyl, R^2 represents 4-fluorophenyl, and R^3 and R^4 each independently represents H, methyl or mesyl.

11. A compound according to claim 10, wherein R^3 is methyl and R^4 is mesyl.

10 12. A process for the preparation of a compound of Formula (2):



Formula (2)

15 which comprises

a) reacting a compound of formula $R^1-CO-CH_2-E$ with a compound of formula $R^2-CHX^1X^2$ in the presence of a compound of formula $R^3R^4N-C(=NH)NH_2$ and a catalyst, thereby to form the compound of Formula (2)

wherein

20 R^1 is an H or an alkyl group;

R^2 is an H or an alkyl or aryl group;

R^3 and R^4 are each independently H, alkyl, aryl, a group of formula $R^5SO_2^-$, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring;

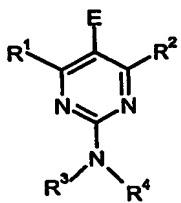
25 E is an electron withdrawing group; and

X^1 and X^2 are each independently leaving groups, or X^1 and X^2 together represent =O.

13. A process according to claim 12, wherein R^1 represents isopropyl, R^2 represents 4-fluorophenyl, and R^3 and R^4 each independently represents H, methyl or mesyl.

30 14. A process according to claim 13, wherein R^3 is methyl and R^4 is mesyl.

15. A process for the preparation of a compound of Formula (1):



Formula (1)

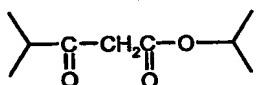
- 5 which comprises oxidising a compound of Formula (2) as claimed in claim 9,
wherein
 R¹ is H or an alkyl group;
 R² is an H, an alkyl or aryl group;
 10 R³ and R⁴ are each independently H, alkyl, aryl, a group of formula R⁵SO₂⁻, wherein R⁵ is
 alkyl or aryl, or R³ and R⁴ are linked to form, together with the nitrogen to which they are
 attached to form a 5 to 7 membered heterocyclic ring; and
 E is an electron withdrawing group.

16. A process according to claim 15, wherein R¹ represents isopropyl, R² represents 4-fluorophenyl, and R³ and R⁴ each independently represents H, methyl or mesyl.

17. A process according to claim 15 or 16, wherein the oxidation employs a quinone.

18. A compound of formula (CH₃)₂CH-CO-CH₂-CO₂-C₃H₇

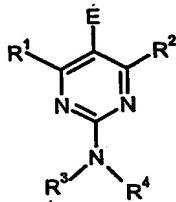
20 19. A compound according to claim 18, of formula:



**ABSTRACT
COMPOUNDS AND PROCESS**

A process for the preparation of a compound of Formula

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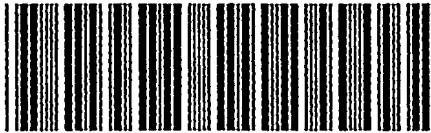
and intermediates useful therein are provided. The process comprises reacting a compound of formula $R^1\text{-CO-CH}_2\text{-E}$ with a compound of formula $R^2\text{-CHX}^1\text{X}^2$ in the presence of a compound of formula $R^3\text{R}^4\text{N-C(=NH)NH}_2$ and a catalyst, thereby to form a dihydropyrimidine; and oxidising the dihydropyrimidine to form the compound of Formula (1). R^1 is H or an alkyl group; R^2 is H, an alkyl or aryl group; R^3 and R^4 are each independently H, alkyl, aryl, a group of formula $R^5\text{SO}_2^-$, wherein R^5 is alkyl or aryl, or R^3 and R^4 are linked to form, together with the nitrogen to which they are attached to form a 5 to 7 membered heterocyclic ring; E is an electron withdrawing group; and X^1 and X^2 are each independently leaving groups, or X^1 and X^2 together represent =O.

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PCT Application

GB0305359



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